REMARKS

Applicant respectfully requests reconsideration of the present application in view of the following remarks.

Status of the Claims

Applicant understands that the claim amendments presented in the response filed August 11, 2010 have been entered. These amendments are reflected in the foregoing Listing of Claims.

No claims are amended, canceled, or added in this Reply. Hence, claims 1, 3-4, 6-7, and 13-18 remain pending and under active consideration in the subject case.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1, 3-7, and 13-17 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Fein (US Publication No. 2004/0138098). Applicant respectfully traverses the rejection.

As reflected in independent claim 1, the claims are directed to a blister pack for pharmaceutical use comprising blisters containing a compressed granulate tablet which tablet comprises a compressed granulate comprising desmopressin, or a pharmaceutically acceptable salt thereof; an acid that provides a pH in the range of from 3.0 to 6.2 as measured when 1 g of said tablet is slurried in 2 ml of water at 25°C; and a pharmaceutically acceptable adjuvant, diluent or carrier.

The Examiner alleges that Fein teaches "blisters" at [0119]; "hard, compressed, rapidly dissolving tablet" comprising desmopressin at [0040]; and a solution having pH 3 to 6 from which the dosages are prepared at [0091]. Leaving aside the fact that the present claims do not encompass a "hard, compressed, rapidly dissolving tablet" (discussed below), the Examiner errs in failing to appreciate that each of the cited features of Fein pertains to an orally absorbable product, such as a thin wafer or film, that is ideally suited for buccal and sublingual administration. Fein, paragraph [0114]. By contrast, the claimed invention is directed to "compressed granulate" tablets that are designed for swallowing.

As will be next explained, the failure of others in the art—despite a long-felt need—to successfully provide a compressed granulate tablet form of desmopressin in blister packaging

would have discouraged any reasonably informed artisan from modifying the teachings of Fein in the manner suggested in the Office Action. In other words, the artisan would have lacked the requisite reason and motivation to modify Fein, which is necessary to properly establish a *prima facie* case of obviousness.

I. No motivation to modify Fein as alleged

As set forth in paragraph [0004] of the instant specification, a conventional "compressed tablet" of desmopressin acetate had been marketed in a blister pack under the trade name Minirin®. The product, however, was withdrawn from the market in 2002 due to a consistent problem with degradation of the desmopressin acetate during long term storage. It is only the present Applicant who determined that "a purposive selection and control of the pH level in a solid dosage form of desmopressin is particularly efficient in counteracting degradation upon storage in blister packs." Paragraph [0011].

Prior to the present invention, the problem of the degradation of desmopressin in the blister packaged Minrin® tablets had not been recognized to be a function of pH, or preventable by controlling pH. Thus, there was no reason to modify the prior art **"compressed tablet"** to arrive at the claimed tablet (*i.e.*, comprising "an acid that provides a pH in the range of from 3.0 to 6.2 as measured when 1 g of said tablet is slurried in 2 ml of water at 25°C").

According to the USPTO's recently released 2010 *KSR* Guideline Update, "[e]ven where a general method that could have been applied to make the claimed product was known and within the level of skill of the ordinary artisan, the claim may nevertheless be nonobvious if the problem which had suggested use of the method had been previously unknown." 70 Fed. Reg. 169, 53646 (Sept. 1, 2010) (citing *In re Omeprazole Patent Litigation*, 536 F.3d 1361 (Fed. Cir. 2008). As noted above, the problem of the degradation of desmopressin in blister packs of Minrin® tablets had not been recognized to be associated with pH; thus the ordinary artisan would have been surprised to discover that compressed granulate tablets, as claimed, can in fact be stably stored in blister packs if the tablets comprise an "acid that provides a pH in the range of from 3.0 to 6.2 as measured when 1 g of said tablet is slurried in 2 ml of water at 25°C."

The unexpected results are illustrated, for example, in Example 3 (PVC blister) and Example 4 (PVC/PVDC blister) at pages 7-8 of the specification, which compare the degradation of desmopressin (upon storage) with respect to compressed granulate tablets with and without an acid as recited in the pending claims. Example 3 demonstrates that the tablet with acid retains 76% of its desmopressin after 7 months of storage as compared to only 52% remaining in the tablet with no acid. Similarly, Example 4 demonstrates that the tablet with acid retains 82% of its desmopressin after 6 months of storage as compared to 76% of desmopressin in the tablet with no acid.

Thus, the present invention solves a significant problem faced by the art, and provides a solution that is not taught or suggested by Fein.

At page 9, the Office Action dismisses this evidence, asserting that the claims are directed to "desmopressin" rather than "desmopressin acetate." This is not correct, however. As explained previously, claim 1 consistently has recited "desmopressin, or a pharmaceutically acceptable salt thereof," which includes desmopressin acetate. To underscore this point, Applicant has added claim 18, which expressly recites the pharmaceutically acceptable salt desmopressin acetate.

Moreover, the Office Action provides no basis for the implied assertion implied that the stability problems observed with the commercial tablet of desmopressin is due to its being an acetate salt, or for the assumption that the problem could have been solved by using desmopressin in its free base form. To the contrary, "the inventors hypothesize [without being bound by a particular theory], that the presence of ***residual moisture*** in solid dosage forms of desmopressin in combination with the increased potential influx of moisture in blister packs (compared *e.g.* to sealed bottles) caused the aforementioned accelerated ***degradation of desmopressin*** upon storage," and that "[t]he presence of moisture in solid dosage forms appears to promote ***dimer formation . . .*** of ***desmopressin.***" [0010] (emphasis added).

II. Each element of the claimed invention is not taught or suggested by Fein

A. A "compressed granulate tablet"

Even assuming, *arguendo*, that the ordinary artisan would have found motivation to modify Fein, the modification would yet fail to arrive at the claimed invention. As noted,

Fein is directed to forms of desmopressin which are absorbed from the mouth, instead of being swallowed. Fein's goal of dissolution in the mouth is inconsistent with compressed granulate tablets as claimed. For this reason, Fein uses Comparative Examples 2 and 3, which describe granulate tablets, in ***contrast*** to its orally absorbable tablets, which are said to be "improved compared to a conventional per oral table formulation (i.e. which is swallowed by the patient.") Paragraph [0026]. Further, Fein teaches that "the need for many conventional processing steps such as granulation and/or the need to purchase more expensive pre-granulated, compressible fillers" may be "***eliminated***" in adopting its dosage forms. *Id.* at [0054] (emphasis added). Thus, Fein does not teach or suggest a compressed granulate tablet as claimed.

Compressed granulate tablets are comprised of compressed ***granules***, while directly compressed tablets simply comprise a compressed form of the original dry component mixture. Thus, it is scientifically ***incorrect*** to equate Fein's "particles" with the recited granules. As explained in the previous response, granulation is a specific manufacturing process whereby the components are "granulated"—formed into small granules—prior to compression into tablet form. In contrast, direct compression is a more simple manufacturing process that involves mixing the dry components and then "directly" compressing them into tablet form. The skilled artisan reviewing Fein would understand that Fein's "particles" are separate and distinct from "granules," and this understanding would be reinforced by Fein's own teachings regarding the avoidance of granulation processes.

In the Advisory Action, the Examiner characterizes this distinction as "method limitations" and thus considers them immaterial to a "composition" claim. In fact, however, these different manufacturing processes result in products that differ at a ***physical*** level.

According to REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, "there are three general methods of tablet preparation: the wet-granulation method, the dry-granulation method, and direct compression." Page 859, col. 2. (attached). The tablets have "attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics, and uniformity, which also are ***influenced by the method of preparation*** and by the added material present in the formulation." Sentence bridging pp 859-60 (emphasis added). Hence, the claim language "compressed granulate tablet" indeed implicates ***physical properties*** of the recited tablets and should be given patentable weight in the present product claims.

For at least the foregoing reasons, Fein's "hard, compressed tablet form" of desmopressin is not a "structural equivalent" of the claimed compressed granulate tablets, let alone anticipatory of the claimed products.

B. A compressed granulate comprising "an acid an acid that provides a pH in the range of from 3.0 to 6.2 as measured when 1 g of said tablet is slurried in 2 ml of water at 25°C"

Fein does not teach or suggest the use of an acid in a compressed granulate tablet where the acid provides a pH in the range of from 3.0 to 6.2 when 1 g of the tablet is slurried in 2 ml of water, as recited in the instant claims.

The Examiner cites Fein's teaching of an acid as a component of an "effervescenet couple," but this does not result in a tablet as claimed. In this embodiment of Fein, an acid source is used in conjunction with a carbon dioxide source, preferably in equivalent ratios. *See, e.g.*, Fein, page 5, paragraph [0062]. Slurrying such a tablet in water would promote reaction between the acid and effervescent agent, resulting in consumption of the acid, not the provision of a desired pH, as claimed.

The Examiner notices that Fein teaches the use of a "pH adjusting agent" to adjust the pH of a solution from which one of Fein's dosage forms is prepared from 3 to 6. [0061, 0091]. But, this teaching is not directed to a "compressed granulate tablet" as claimed. Rather, this teaching of Fein is made in the context of its freeze-dried orodispersible dosage form, which is still further afield from the claimed compressed granulate tablets.

Thus, Fein does not provide any teaching that anticipates or renders obvious this aspect of the claimed product.

C. A compressed granulate tablet in "blister" packs

Fein also fails to teach a blister comprising a "compressed granulate tablet" as claimed. The Examiner cites the disclosure of blister packaging Example 1 of Fein. However, this disclosure pertains only to freeze-dried "intrabuccally disintegrating [orodispersible] solid formulations," which are not compressed tablets of any kind. *See, e.g.*, Fein, page 8, paragraphs [0092] and [0093]. As for "hard, compressed, rapidly dissolving tablet[s]", Fein expressly teaches storing them directly in bulk, *i.e.*, not in a blister pack. *See, e.g.*, Fein, page 3, paragraph [0040].

The Advisory Action alleges that it would have been "well within the purview" of the skilled artisan to package Fein's tablets in blister packs, but this ignores the known problems encountered when conventional desmopressin tablets are packaged in blister packs that led to the withdrawal of blister packaged Minrin® tablets from the market. Since Fein neither addresses nor solves this problem, the skilled artisan would have been discouraged from returning to the same type of packaging for any type of desmopressin ***tablets***. Indeed, Fein's own decision to describe blister packaging in the context of its freeze-dried formulation but ***not*** its tablet formulation reflects the understanding in the art that ***blister packaging was not suitable for desmopressin tablets***.

As noted above and discussed in the instant application, it is only the present inventors who surprisingly discovered that the recited compressed granulate tablets exhibit unexpected stability when stored in blister packs. For example, paragraph [0011] teaches that "it has been found that a purposive selection and control of the pH level in a solid dosage form of desmopressin is particularly efficient in counteracting degradation upon storage in blister packs." Thus, it is only the present invention that addresses and solves the significant problem faced by the art, and provides a solution that is not taught or suggested by Fein.

In view of the foregoing, Applicant respectfully urges reconsideration and withdrawal of the pending §103 rejection.

CONCLUSION

Applicant believes that the application is in condition for allowance, and an early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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